

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Tsuyoshi NAGANUMA et al

Application No.: 10/538,514

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Group Art Unit: 4133

For: SOLID DRUG FOR ORAL USE

Examiner: Walter E. Webb

DECLARATION UNDER 37 C.F.R 1.132

Honorable Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Tsuyoshi NAGANUMA of 4622-38, Toyoshina, Azumino-shi, Nagano 399-8205 JAPAN, being duly sworn, declare and state:

THAT I am by profession a research chemist having a bachelor's degree in industrial chemistry from Chuo University in March 1990.

THAT I have been employed since April 1990 by Kissei Pharmaceutical Co., Ltd. of 19-48, Yoshino, Matsumoto-shi, Nagano 399-8710 JAPAN and engaged in engineering and research mainly on:

production on drug products in the production department of the same company from April 1990 to September 1990; and then formulation technology studies on drug products in Central Research Laboratories of the same company from October 1990 up to now.

THAT I am one of co-inventors of the invention disclosed in the above-identified U.S. patent application and hence I am fully familiar therewith.

In order to demonstrate that the present invention is not obvious over Kitazawa in view of Ishihara and in further view of Salpekar and Shar, we have conducted the following experiments.

#### Experiment

1. Preparation of (1) capsules of Examples 1, 2, 2A and 2B of the present invention, and (2) comparative capsules of Capsules A, B, H, N, O, F, P, 1A, 1B, 2A and 2B

(1) Capsules of Examples 1, 2, 2A and 2B of the present invention, and (2) Capsules of comparative examples of Capsules A, B, H, N, O, F, P, 1A, 1B, 2A and 2B were prepared for evaluating their dissolution property and manufacturing aptitude.

#### Example 1

In accordance with the procedures as described in Example 1 on page 34 in the present specification, a capsule of Example 1 was prepared as follows.

A mixture of KMD-3213 (320 g), D-mannitol (21,504 g), partially pregelatinized starch (PCS, 4,160 g) and partially pregelatinized starch (Starch 1500, 1,440 g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium

stearate (288g) and sodium lauryl sulfate (288 g) was added thereto, mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 2.0 mg of KMD-3213.

In preparing the capsules of Example 1, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

#### Example 2

In accordance with the procedures as described in Example 2 on page 35 in the present specification, a capsule of Example 2 was prepared as follows.

A mixture of KMD-3213 (640 g), D-mannitol (21,184 g), partially pregelatinized starch (PCS, 4,160 g) and partially pregelatinized starch (Starch 1500, 1,440 g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium stearate (288 g) and sodium lauryl sulfate (288 g) was added thereto, mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

In preparing the capsules of Example 2, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

#### Example 2A

In accordance with the formulation of Example 2A in Table 1, a capsule of Example 2A was prepared as follows.

A mixture of KMD-3213 (36 g), D-mannitol (1,191.6 g), partially pregelatinized starch (PCS, 234 g), and partially pregelatinized starch (Starch 1500, 81 g) were mixed

sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Calcium stearate (14.4 g) and sodium lauryl sulfate (14.4 g) were added to the granule (1,371.2 g), mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

In preparing the capsules of Example 2A, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

#### Example 2B

In accordance with the formulation of Example 2B in Table 1, a capsule of Example 2B was prepared as follows.

A mixture of KMD-3213 (36 g), D-mannitol (1,191.6 g), partially pregelatinized starch (PCS, 234 g), and partially pregelatinized starch (Starch 1500, 81 g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Talc (14.4 g) and sodium lauryl sulfate (14.4 g) were added to the granule (1,371.2 g), mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

In preparing the capsules of Example 2B, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

#### Capsule A

In accordance with the formulation of Capsule A in Table 4 on page 32 in the present specification, a capsule of Capsule

A was prepared as follows.

A mixture of KMD-3213 (32 g), D-mannitol (1,353.6 g), and partially pregelatinized starch (Starch 1500, 80 g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. The granule was filled into a Capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

In preparing the capsules of Capsule A, a filling trouble such as sticking was observed during encapsulating process.

#### Capsule B

In accordance with the formulation of Capsule B in Table 4 on page 32 in the present specification, a capsule of Capsule B was prepared as follows.

A mixture of KMD-3213 (32 g), D-mannitol (1,353.6 g), and partially pregelatinized starch (Starch 1500, 80 g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (12.6 g) was added to the granule (1,282.4 g), mixed for 10 minutes, and filled into a capsule shell to prepare a Capsule containing 4.0 mg of KMD-3213.

In preparing the capsules of Capsule B, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

#### Capsule H

In accordance with the formulation of Capsule H in Table 5 on page 34 in the present specification, a capsule of Capsule H was prepared as follows.

A mixture of KMD-3213 (20 g), D-mannitol (1,344 g), partially pregelatinized starch (PCS, 260 g) and partially pregelatinized starch (Starch 1500, 90 g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (10.8 g) was added to the granule (1,028.4 g), mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 2.0mg of KMD-3213.

In preparing the capsules of Capsule H, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

#### Capsule N

In accordance with the formulation of Capsule N in Table 1, a capsule of Capsule N was prepared as follows.

A mixture of KMD-3213 (80 g) and partially pregelatinized starch (Starch 1500, 200 g) were mixed sufficiently. The mixture was granulated with water. The granule was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (12.6 g) was added to the sieved granules (98 g) and mixed for 3 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

#### Capsule O

In accordance with the formulation of Capsule O in Table 1, a capsule of Capsule O was prepared as follows.

A mixture of KMD-3213 (80 g) and partially pregelatinized starch (Starch 1500, 200 g) were mixed sufficiently. The mixture was granulated with water. The granule was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (12.6 g) and sodium lauryl sulfate (12.6 g) were added to the sieved granules (98 g) and mixed for 3 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

#### Capsule F

In accordance with the formulation of Capsule F in Table 4 on page 32 in the present specification, a capsule of Capsule F was prepared as follows.

A mixture of KMD-3213 (36 g), D-mannitol (1522.8 g), and partially pregelatinized starch (Starch 1500, 90 g) were mixed sufficiently, and kneaded with an appropriate amount of water to granulate. The granulated material was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. A mixture of magnesium stearate (9.9 g) and Light Anhydrous Silisic Acid (9.9 g) were added to the granule (1,007.6 g), mixed for 5 minutes, and filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

In preparing the capsules of Capsule F, no filling trouble was observed during encapsulating process, and good manufacturing aptitude was achieved.

#### Capsule P

In accordance with the formulation of Capsule P in Table 2, a capsule of Capsule P was prepared as follows.

A mixture of KMD-3213 (6.4 g), Lactose (227.52 g), and partially pregelatinized starch (Starch 1500, 59.2 g) were mixed sufficiently. The mixture was granulated with water. The granule was dried using a fluid bed drier at an inlet air temperature of 60 °C until the exhaust air reaches 40 °C, and sieved. Magnesium stearate (1.08 g) was added to the sieved granules (109.92 g) and mixed for 3 minute, and the mixture was filled into a capsule shell to prepare a capsule containing 4.0 mg of KMD-3213.

In order to compare the dissolution rate of the capsule of the present invention with a formulation suggested by Salpekar, we have prepared a capsule containing KMD-3213 instead of acetaminophen; pregelatinized starch; povidone; and stearic acid according to the composition of Example 1 as described in Salpekar (US4,757,090) as follows. Since salpekar does not disclose specifically what type of pregelatinized starch can be used, we used Starch 1500 suggested by Shar.

#### Capsules 1A and 1B

A mixture of KMD-3213 (9.0 g), partially pregelatinized starch (Starch 1500, 0.85 g) and povidone (0.1 g) was mixed sufficiently. The mixture was granulated with water. The granule was dried using a Static Solid bed drier at an inlet air temperature of about 70 °C for 2 hours, and sieved. Stearic acid (0.05 g) was added to the sieved granules and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a Capsule 1A containing 4.0 mg of KMD-3213.

Furthermore, sodium lauryl sulfate (0.05 g) was added to the lubricated granules containing stearic acid and mixed for 1

minute, and the mixture was filled into a capsule shell to prepare a Capsule 1B containing 4.0 mg of KMD-3213.

In order to compare the dissolution rate of the capsule of the present invention with a formulation suggested by Shar, we have prepared a capsule containing KMD-3213 instead of acetaminophen; partially pregelatinized starch (Starch 1500); povidone (K-90); croscarmellose sodium (Ac-Di-Sol); stearic acid; and colloidal silicon dioxide according to the composition of Example 1 as described in Shar (US5,370,878) as follows.

#### Capsules 2A and 2B

A mixture of KMD-3213 (9.0 g), partially pregelatinized starch (0.35 g), croscarmellose sodium (0.2 g) and povidone (0.2 g) was mixed sufficiently. The mixture was granulated with water. The granule was dried using a Static Solid bed drier at an inlet air temperature of about 70 °C for 2 hours, and sieved. Colloidal silicon dioxide (0.05 g) and stearic acid (0.2 g) were added to the sieved granules and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a Capsule 2A containing 4.0 mg of KMD-3213.

Furthermore, sodium lauryl sulfate (0.2 g) was added to the lubricated granules containing stearic acid and colloidal silicon dioxide and mixed for 1 minute, and the mixture was filled into a capsule shell to prepare a Capsule 2B containing 4.0 mg of KMD-3213.

## 2. Dissolution test

In accordance with the procedures of "Dissolution Test Method" as described in Test Example 4 in the present specification, the capsules of Examples 1, 2, 2A and 2B of the

present invention; and the comparative capsules of Capsules A, B, H, N, O, F, P, 1A, 1B, 2A and 2B were tested. The results are shown in Tables 1 and 2.

We have shown Tablets 1 and 2 in Table 2 in which Tablet 1 is a formulation as disclosed in Example 1 of Salpekar (US4,757,090) and Tablet 2 is a formulation as disclosed in Example 1 of Shar (US5,370,878).

Table 1

Capsule	the present invention			Comparative example					
	Example 2	Example 2A	Example 2B	Capsule A	Capsule B	Capsule H	Capsule N	Capsule O	Capsule F
KMD-3213	4.0	4.0	4.0	4.0	4.0	2.0	4.0	4.0	4.0
D-Mannitol	132.4	132.4	132.4	169.2	169.2	134.4			169.2
Partially pregelatinized starch (PCS)	26.0	26.0	26.0			26.0			
Partially pregelatinized starch (Starch 1500)	9.0	9.0	9.0	10.0	10.0	9.0	10.0	10.0	10.0
Magnesium stearate	1.8				1.8	1.8	1.8	1.8	1.8
Calcium stearate		1.8							
Talc			1.8						
Light anhydrous silicic acid									1.8
Sodium lauryl sulfate	1.8	1.8	1.8					1.8	
total weight (mg/Capsule)	175.0	175.0	175.0	183.2	185.0	173.2	15.8	17.6	186.8
Dissolution rate (%) after 15 minutes	97	93	95	85	8	23	0.6	32	9
Filling problem during encapsulation	none	none	none	sticking	none	none	not tested	not tested	none

Table 2

Capsule	the present invention		Comparative example						Cited documents	
	Example 1	Example 2	Capsule P	Capsule 1A	Capsule 1B	Capsule 2A	Capsule 2B	Tablet 1 (Salpekar)	Tablet 2 (Shar)	
KMD-3213	2.0	4.0	4.0	4.0 (90.0)	4.0 (90.0)	4.0 (90.0)	4.0 (90.0)			
Acetaminophen								(90.0)	(90.0)	
D-Mannitol	134.4	132.4								
Lactose			142.2							
Partially pregelatinized starch (PCS)	26.0	26.0								
Partially pregelatinized starch (Starch 1500)	9.0	9.0	37	0.378 (8.5)	0.378 (8.5)	0.156 (3.5)	0.156 (3.5)	pregelatinized starch (8.5)	(3.5)	
Croscarmellose Sodium (Ac-Di-Sol)						0.089 (2.0)	0.089 (2.0)		(2.0)	
Povidone (K-30)				0.044 (1.0)	0.044 (1.0)			(1.0)		
Povidone (K-90)						0.089 (2.0)	0.089 (2.0)		(2.0)	
Magnesium stearate	1.8	1.8	1.8							
Sodium lauryl sulfate	1.8	1.8			0.022 (0.5)		0.089 (2.0)			
Stearic acid				0.022 (0.5)	0.022 (0.5)	0.089 (2.0)	0.089 (2.0)	(0.5)	(2.0)	
Colloidal silicon dioxide						0.022 (0.5)	0.022 (0.5)		(0.5)	
total weight (mg/Capsule)	175.0	175.0	185	4.444 (100.0)	4.466 (100.5)	4.445 (100.0)	4.534 (102.0)	(100.0)	(100.0)	
Dissolution rate (%) after 15 minutes	93	97	6	9	16	12	16	>80% after 20min.	rapid dissolution	

numeric value in parentheses: ratio

1. Difference of physicochemical property between KMD-3213 and Acetaminophen

Comparison of the dissolution rates of Tablets 1 and 2 containing Acetaminophen with those of Capsules 1A and 2A containing KMD-3213 instead of Acetaminophen shows that Tablets 1 and 2 containing Acetaminophen exhibit rapid dissolution rates while Capsules 1A and 2A containing KMD-3213 exhibit notably low dissolution rates.

It has been reported that Acetaminophen has a water solubility of 14 mg/mL at 20°C from the data base of CAS 103-90-2 while KMD-3213 has a water solubility of 0.17 mg/mL at 20°C. Acetaminophen has approximately a 100 times higher water solubility as compared with that of KMD-3213.

It is generally known that the dissolution properties of drugs are well correlated to their water solubilities. From the results of the dissolution tests in Table 2, we believe that those ordinarily skilled in the art would easily understand that the notable difference of the dissolution rates between KMD-3213 and Acetaminophen results from their physicochemical properties such as water solubility and the like.

2. Regarding partially pregelatinized starch/ pregelatinized starch

In the previous Declaration submitted on July 22, 2009, we have shown the results of the dissolution test on Capsules 1A, 1B, 2A and 2B containing KMD-3213 instead of Acetaminophen, all of which exhibited only less than 20% dissolution rate. From those results, we have argued that the general mention regarding pregelatinized starch in Salpekar does not teach the immediate dissolution property exhibited by the capsules of the present invention.

To the arguments, the examiner states in the final rejection on October 08, 2009 that "salpekar et al. teach a composition and a direct tableting process, where pregelatinized starch is included in an amount effective for imparting to the composition a short dissolution time, e.g. about 20 minutes or less for 80% or more of the active compound to dissolve."

However, Salpekar refers only to pregelatinized starch, but does not teach partially pregelatinized starch. The term "pregelatinized starch" includes partially and completely pregelatinized starch. Salpekar fails to teach or suggest what type of pregelatinized starch imparts to the composition such a short dissolution time. On the contrary, Shar refers to partially or completely pregelatinized starch as a binder, but fails to teach or suggest any special dissolution effects due to partially or completely pregelatinized starch.

Accordingly, the Salpekar teaching of a short dissolution time, e.g., about 20 minutes or less for 80% or more of the APAP to dissolve, which is achieved with pregelatinized starch, would not lead those ordinarily skilled in the art to expect the immediate dissolution property exhibited by the capsules of the present invention. In fact, the dissolution rate of Capsule P, which corresponds to a capsule containing partially pregelatinized starch (Starch 1500) instead of corn starch in the tablet of Formulation Example 1 on page 51 in Ishihara, is only 6% as shown in table 2 in this Declaration.

Futhermore, Salpekar, Shar, Ishihara and Kitazawa fail to teach or suggest a combination use of two types of partially pregelatinized starch consisting of Starch 1500 and PCS.

Regarding the results of Capsules 1A, 1B, 2A and 2B, the examiner also states that "it is clear from Salpekar that the

amount of pregelatinized starch depends on the expected result". However, as shown in the dissolution rates of Capsules B, H, N and O in Table 1, Capsules B, H, N and O, which contains the same amount of Starch 1500 as the capsule of Example 2, or Capsule H, which contains the same amount of Starch 1500 and PCS as the capsule of Example 2, exhibit only low dissolution rates.

The rapid dissolution properties of the Capsules of the present invention can be achieved by containing all of the four components of a) D-mannitol, b) two types of partially pregelatinied starch consisting of Starch 1500 and PCS, c) a lubricant slected from magnesium stearate, calcium stearate and talc, and d) sodium lauryl sulfate. Even in the case of containing the same amount of partially pregelatinized starch, Capsules B, H, N and O not containing at least one component of D-manitol or sodium lauryl sulfate exhibit notably low dissolution rates.

### 3. Regarding lubricant/sodium lauryl sulfate

The examiner states that "Salpekar teaches adding compatible mixtures of two or more lubricants such as sodium lauryl sulfate, magnesium stearate". However, Capsules O, 1B and 2B, which contain sodium lauryl sulfate and other lubricant but does not contain D-mannitol, exhibit only low dissolution rates.

The examiner also states that "These amount are such that disintegration, dissolution time will not be increased". However, the description that dissolution time will not be increased does not teach that dissolution time will be decreased. Salpekar fails to teach or suggest what combination of lubricants could be used for imparting to the composition a decreased dissolution time.

Shar teaches colloidal silica and stearic acid as a preferable lubricant on column 4, lines 19-20 and TABLE I. Capsule F in Table 1 contains such a preferable silicon dioxide and magnesium stearate. However, the dissolution rate of the Capsule F is as low as that of Capsule B containing only magnesium stearate.

On the contrary, the dissolution rate of the capsule of Example 2 containing magnesium stearate and sodium lauryl sulfate is remarkably higher as compared with that of Capsule H. The teaching of Salpekar and Shar regarding lubricants would not lead those ordinarily skilled in the art to expect such a remarkable improving effect on the dissolution rate achieved by a particular combination use of sodium lauryl sulfate and magnesium stearate.

Regarding the scope of the lubricants as claimed in the present claim 1, we submit the results of dissolution rates of Example 2A containing calcium stearate and Example 2B containing talc. The dissolution rates of the capsules of Examples 2A and 2B are as high as that of Example 2 containing magnesium stearate.

#### 4. Regarding manufacturing aptitude

In the previous Declaration, we have argued that "Ishihara fails to teach or suggest how to achieve immediate dissolution properties and good manufacturing aptitude without causing filling problems during encapsulating process at the same time".

To the arguments, the examiner state that "Ishihara was used to show that light-shielding coating such as titanium oxide, D-mannitol, magnesium stearate, and sodium lauryl sulfate were

known to be useful in formulating a Capsule for KMD-3213". However, the description of "D-mannitol, magnesium stearate, and sodium lauryl sulfate were known to be useful in formulating a Capsule" teaches only that bulking agents such as D-mannitol, or lubricants such as magnesium stearate and sodium lauryl sulfate could be available as an ingredient for formulating a capsule.

KMD-3213 is hardly soluble in water and has a strong adhesive property and is apt to be charged with static electricity which causes filling problems during encapsulating process. It is an extremely unobvious effect that the capsule of the present invention comprising a) D-mannitol, b) two types of partially pregelatinized starch consisting of Starch 1500 and PCS, c) a lubricant selected from magnesium stearate, calcium Stearate and talc, and d) sodium lauryl sulfate exhibit immediate dissolution properties and has good manufacturing aptitude without causing filling problems during encapsulating process at the same time.

As discussed above, Kitazawa, Ishihara, Salpekar and Shar fail to teach or suggest how to improve dissolution properties in water in which KMD-3213 is hardly soluble and how to resolve filling problems caused by the adhesive property of KMD-3213 during encapsulating process at the same time.

Therefore, we believe that the capsules of the present invention are not obvious over Kitazawa in view of Ishihara and in further view of Salpekar and Shar.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 15, 2010

Tsuyoshi Naganuma  
Tsuyoshi NAGANUMA